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ORIGINAL ARTICLE

Exposure–response modeling of peficitinib efficacy in patients with rheumatoid arthritis

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Abstract

The aim was to analyze the relationship between peficitinib exposure and efficacy response according to American College of Rheumatology (ACR) 20 criteria and 28-joint disease activity score based on C-reactive protein (DAS28-CRP) in rheumatoid arthritis (RA) patients, and to identify relevant covariates by developing exposure–response models. The analysis incorporated results from three multicenter, placebo-controlled, double-blind studies. As an exposure parameter, individual post hoc pharmacokinetic (PK) parameters were obtained from a previously constructed population PK model. Longitudinal ACR20 response rate and individual longitudinal DAS28-CRP measurements were modeled by a non-linear mixed effect model. Influential covariates were explored, and their effects on efficacy were quantitatively assessed and compared. The exposure–response models of effect of peficitinib on duration-dependent increase in ACR20 response rate and decrease in DAS28-CRP were adequately described by a continuous time Markov model and an indirect response model, respectively, with a sigmoidal E_{max} saturable of drug exposure in RA patients. The significant covariates were DAS28-CRP and total bilirubin at baseline for the ACR20 response model, and CRP at baseline and concomitant methotrexate treatment for the DAS28–CRP model. The covariate effects were highly consistent between the two models. Our exposure–response models of peficitinib in RA patients satisfactorily described duration-dependent improvements in ACR20 response rates and DAS28-CRP measurements, and provided consistent covariate effects. Only the ACR20 model incorporated a patient's subjective high expectations just after the start of the treatment. Therefore, due to their similarities and differences, both models may have relevant applications in the development of RA treatment.

Clinical trial registration: NCT01649999 (RAJ1), NCT02308163 (RAJ3), NCT02305849 (RAJ4).

KEYWORDS
modeling and simulation, pharmacometrics, population analysis, rheumatoid arthritis

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What is already known about this subject?

- Efficacy of peficitinib for rheumatoid arthritis (RA) treatment, using American College of Rheumatology (ACR) 20 criteria and 28-joint disease activity score based on C-reactive protein (DAS28-CRP), was assessed in phase 2 and 3 studies.
- The exposure–response relationship for peficitinib in RA patients is unknown, and covariates have not been explored.

What this study adds?

- We constructed exposure–response models of peficitinib efficacy in RA patients to predict ACR20 response rate and DAS28-CRP measurements.
- In both models, baseline disease severity was a significant covariate, and covariate effects were consistent.
- Given their characteristics, both models may have relevant applications in the development of RA treatments.

Brief summary of most exciting findings of research

Two exposure–response models were constructed to predict the effect of peficitinib on ACR20 response rate and DAS28-CRP in patients with RA.

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disease that targets the synovial tissues.[1,2] Disease-modifying antirheumatic drugs (DMARDs) have an important role in inhibiting disease progression; in patients who respond inadequately or are intolerant to conventional synthetic (cs)DMARDs, biological (b) DMARDs and targeted synthetic (ts)DMARDs are recommended as part of combination therapy.[3,4] However, unmet therapeutic needs in RA remain: for example, 30–40% of patients are unresponsive to bDMARDs.[5] It is therefore crucial to develop alternative treatments for patients with RA and an inadequate response to existing drugs.

Peficitinib is an orally bioavailable inhibitor of the Janus kinase (JAK) family: JAK1, JAK2, JAK3, and tyrosine kinase 2.[6] The JAK/signal transduction and activator of transcription (STAT) signaling pathway is implicated in the pathogenesis of inflammatory and autoimmune diseases, and is thus a therapeutic target to treat RA.[6-8]

The efficacy and safety of peficitinib, as monotherapy or in combination with csDMARDs, for treatment of patients with RA have been demonstrated previously in phase 2 and phase 3 randomized, double-blind, placebo-controlled studies conducted in Asian countries (Japan, Korea, and Taiwan).[9-11] Peficitinib has been approved in Japan, Korea, and Taiwan as an RA treatment in patients who have an inadequate response to conventional DMARD therapy.[12-16] Previously, prior exposure–response models were developed using the result of the phase 2 study[9] and the results from these supported the rationale behind the dosing used in the phase 3 studies[10,11] (not published).

The objectives of this study were a) to develop exposure–response models using the results from the phase 2 and phase 3 studies[9-11] for the relationship between peficitinib exposure and two efficacy outcomes: American College of Rheumatology (ACR) 20 criteria and 28-joint disease activity score based on C-reactive protein (DAS28-CRP), which were the primary and one of the secondary endpoints, respectively, in the phase 2 and 3 studies[9-11]; b) to explore the relevant covariates underlying the differences in clinical response; and c) to clarify the similarities and differences of the two models, in order to reveal the optimal use of peficitinib in patients with RA.

2 | METHODS

2.1 | Design of the clinical studies

For this exposure–response analysis of peficitinib treatment for RA, the results from three multicenter, placebo-controlled, double-blind studies were included (the RAJ1 phase 2 study[9] and the RAJ3 and RAJ4 phase 3 studies[10,11]). Study designs, treatment arms, and time points for assessment of ACR20, DAS28-CRP, and peficitinib plasma concentrations are summarized in Table **1**. All clinical studies were conducted in accordance with ethical principles of the Declaration of Helsinki, Good Clinical Practice, and the International Conference for Harmonization guidelines, and were approved by the relevant institutional review boards. All patients provided written informed consent.

2.2 | Exposure parameters

A population pharmacokinetic (PK) model for peficitinib in RA patients was previously constructed as a two-compartment model with sequential zero- and first-order absorption and lag time using NONMEM®.[17] This model was utilized to obtain individual post hoc

TABLE 1 Peficitinib clinical studies included in the analysis

Study number (Clinical Trials.gov identifier)	Indication	Study design	Treatment	No. of patients[a]	Treatment duration (weeks)	Assessment time points				Ref.
						ACR20 response	DAS28-CRP	Peficitinib plasma trough concentrations	Peficitinib concentrations post-administration	
RAJ1 (NCT01649999)	RA; no concomitant or recent DMARD therapy	Phase 2b, randomized, double-blind, placebo-controlled, parallel-group	Placebo, 25 mg, 50 mg, 100 mg, 150 mg	281	12	Weeks 1, 2, 4, 8, and 12	Baseline and weeks 1, 2, 4, 8 and 12	Weeks 1, 2, 4, 8 and 12	N/A	9
RAJ3 (NCT02308163)	RA; inadequate response to, or intolerance of, prior DMARDs, including MTX	Phase 3, randomized, double-blind, placebo-controlled, active-referenced, parallel-group	Placebo to 100 mg or 150 mg at Week 12, 100 mg, 150 mg, open-label etanercept[b]	307	52	Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52	Baseline and every 4 weeks until 52 weeks	Weeks 4, 8, 12, 20, 28, 40, and 52	Week 4 or 8	10
RAJ4 (NCT02305849)	RA; inadequate response to MTX	Phase 3, randomized, double-blind, placebo-controlled, parallel-group	Placebo to 100 mg or 150 mg at Week 12 or 28[c], 100 mg, 150 mg	518	52	Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52	Baseline and every 4 weeks until 52 weeks	Weeks 4, 8, 12, 20, 28, 40, and 52	Week 4 or 8	11

Abbreviations: ACR, American College of Rheumatology; DAS28-CRP, 28-joint disease activity score based on C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; IR, inadequate response; MTX, methotrexate; N/A, not available; PK, pharmacokinetic; RA, rheumatoid arthritis.

[a]Total number of patients who received at least one dose of the study drug.

[b]Patients receiving etanercept were excluded from the analysis.

[c]Inadequate responders in the placebo group were switched to either peficitinib 100 or 150 mg at week 12, and the remaining patients in placebo group were switched to peficitinib 100 or 150 mg at week 28.

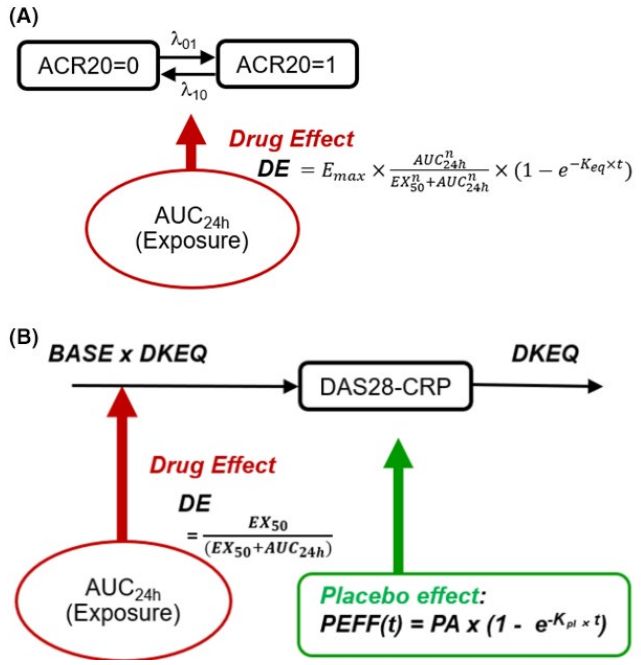

FIGURE 1 Structure of exposure–response models: (A) ACR20 model, and (B) DAS28-CRP model. ACR, American College of Rheumatology; $AUC_{24\,h}$, area under the plasma concentration–time curve for the 24-hour period after dosing; BASE, DAS28-CRP at baseline; CRP, C-reactive protein; DAS, 28-joint disease activity score; DE, positive drug effect on the transition rates in ACR20 model or drug effect in DAS28-CRP model; DKEQ, production rate constant of disease severity; E_{max}, maximum effective response; EX_{50}, drug exposure in $AUC_{24\,h}$ to provide the half-maximal effect; K_{eq}, equilibrium rate constant to reach the steady-state effect; K_{pl}, rate constant to reach maximum placebo effect; n, Hill coefficient for the sigmoidal shape; PA, maximum placebo effect; PEFF, placebo effect, t, number of weeks after the first administration of study drug; λ_{01}, transition constant for transition from state 0 to state 1; λ_{10}, transition constant for transition from state 1 to state 0

area under the plasma concentration–time curve for the 24-hour period after dosing ($AUC_{24\,h}$) at steady state, based on the concentrations obtained in the above phase 2 and phase 3 studies, as an exposure parameter for this analysis.

2.3 | ACR20 model

A longitudinal ACR20 response rate per treatment arm was modeled (Figure 1-A). Individual missing ACR20 responses were not imputed. Unlike the primary statistical analyses,[9-11] right-censored ACR20 responses due to premature termination were neither imputed nor used for the analyses, regardless of the reason for the termination. Patients with only one ACR20 response were excluded from the analysis because of the inability to construct a model from these data. ACR20 responses recorded after week 28 in patients in the RAJ4 study who continued to receive placebo by week 28 without drop-out were excluded to avoid introducing upward bias in placebo response. Outliers were not defined throughout the modeling.

A continuous time Markov model[18] was applied to describe the probability of longitudinal ACR20 response rates. The rate constants for the transition between responding state (1) and non-responding state (0) are defined in Equations 1 and 2:

$$\lambda_{01} = \exp(\alpha_0 + DE) \quad (1)$$

$$\lambda_{10} = \exp(\alpha_1 - DE) \quad (2)$$

where λ_{01} and λ_{10} are the transition constants for transitions from state 0 to state 1 and from state 1 to state 0, and α_0/α_1 and DE are the intercepts and positive drug effect on the transition rates, respectively. The drug effect was assumed to have a sigmoidal maximum effective response (E_{max}) type intensity with time delay to reach the steady-state effect, as shown in Equation 3:

$$DE = E_{max} \times \frac{AUC_{24h}^{n}}{EX_{50}^{n} + AUC_{24h}^{n}} \times (1 - e^{-K_{eq} \times t}) \quad (3)$$

where EX_{50}, K_{eq}, and n are drug exposure in $AUC_{24\,h}$ to provide the half-maximal effect, the equilibrium rate constant to reach the steady-state effect, and the Hill coefficient for the sigmoidal shape, respectively. Time (t) is defined as the number of weeks after the first administration of study drug. Probabilities of the transitions between the states are shown in Equations 4 to 7:

$$p_{01} = \frac{\lambda_{01}}{\lambda_{01} + \lambda_{10}}(1 - \exp(-(\lambda_{01} + \lambda_{10})) \times \delta) \quad (4)$$

$$p_{00} = 1 - p_{01} \quad (5)$$

$$p_{10} = \frac{\lambda_{10}}{\lambda_{01} + \lambda_{10}}(1 - \exp(-(\lambda_{01} + \lambda_{10})) \times \delta) \quad (6)$$

$$p_{11} = 1 - p_{10} \quad (7)$$

where p_{ab} and δ are the probabilities of transition from previous state (a = 0: non-responding state or a = 1: responding state) to the consecutive current state (b = 0: non-responding state or b = 1: responding state) and duration between the observations, respectively. ACR20-CRP at baseline was set to zero. Additive interindividual variability (IIV) was assumed in λ_{01} to describe IIV sensitivity to drug effect.

For assessment visits less than 4 weeks after the first administration of study drug (RAJ1 study only), a higher probability of transitioning to a responder from a non-responder (p^{01}) was assumed, which was equal to a probability of becoming a responder from a responder (p^{11}), in order to account for the patient's high expectations of treatment during a clinical trial. A non-linear mixed effect model was constructed with NONMEM® version 7.3 software (ICON, Ellicott City, MD, USA) using the first-order conditional estimation method with the Laplacian likelihood option.

2.4 | DAS28-CRP model

Individual longitudinal DAS28-CRP measurements were modeled (Figure 1-B). Missing DAS28-CRP measurements were not imputed and patients who had only one DAS28-CRP measurement or no DAS28-CRP measurement at baseline were excluded from the analysis. Outliers were not defined throughout the modeling.

An indirect response model[19] incorporating the inhibitory effect of the drug on the production rate constant of disease severity was applied to describe the time course of DAS28-CRP, as shown in Equation 8:

$$\frac{dDAS28-CRP(t)}{dt} = BASE \times DKEQ \times DE - DKEQ \times DAS28-CRP(t) \quad (8)$$

where BASE, DKEQ, and DE are the DAS28-CRP at baseline, production rate constant of disease severity, and drug effect, respectively. The drug effect on the production rate constant was assumed to have a sigmoidal E_{max} type intensity, as shown in Equation 9:

$$DE = E_{max} \times \frac{EX_{50}}{EX_{50} + AUC_{24h}} \quad (9)$$

E_{max} was assumed to be 1, as it was estimated to be close to 1 in the preliminary analysis. Moreover, the placebo effect (PEFF) was added to the effect obtained from Equation 8 by exponentially increasing or decreasing change with time, as shown in Equation 10:

$$PEFF(t) = PA \times (1 - e^{-K_{pl} \times t}) \quad (10)$$

where PA and K_{pl} are the maximum placebo effect and rate constant to reach maximum placebo effect, respectively. IIV of EX_{50} for sensitivity to drug effect was assumed to have log-normal distribution. IIV of PA was defined as an additive to allow both upward and downward time courses during placebo treatment. Residual random effect was included as an additive variance. A non-linear mixed effect model was constructed with NONMEM software using the first-order conditional estimation method with interaction option (FOCEI).

2.5 | Covariate exploration

In both the ACR20 and DAS28-CRP models, the effect on EX_{50} of the following candidate covariates was investigated: demographics; laboratory test values at baseline; disease activity at baseline; prior treatment for RA; history of inadequate response to prior treatment; and use of concomitant medication. Details of the covariates investigated are listed in Table 2.

The candidate covariates were evaluated as target covariates with significant decrease in objective functional value (OFV) (6.64) by adding one candidate covariate at a time in the base model. For target covariates, the covariate exploration was undertaken using stepwise forward addition (significance level $p < 0.01$) followed by backward elimination (significance level $p < 0.001$). The relationship between covariates having continuous value and PK parameters was modeled using a power function centralized by a representative value as arithmetic mean of the covariates (Equation 11):

TABLE 2 List of candidate covariates

Category	Candidate covariates (units)
Demographics	Age (years), BMI (kg/m^2), BSA (m^2), LBM (kg), weight (kg), gender
Laboratory test values at baseline	Serum albumin (g/L), ALT (U/L), AST (U/L), ALP (U/L), total bilirubin (μmol/L), CPK (U/L), total protein (g/L), tLDL cholesterol (mmol/L), creatinine (μmol/L), urate (μmol/L), teGFR (mL/min/1.73^2), hematocrit, hemoglobin (g/L), terythrocyte count (10^{12}/L), lymphocyte count (10^6/L), tabsolute neutrophil count (10^6/L), platelets count (10^9/L)
Disease severity at baseline	CRP (mg/L), ESR (mm/h), DAS28-CRP, DAS28-ESR, HAQ-DI score, SDAI, RA duration (years), stage of RA[a]
Prior treatment	bDMARDs, TNF inhibitors
History of inadequate response to prior treatment	MTX, bDMARDs, csDMARDs
Concomitant medication	csDMARDs, MTX, steroids, prednisolone

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; b, biological; BMI, body mass index; BSA, body surface area; CPK, creatinine kinase; CRP, C-reactive protein; cs, conventional synthetic; DAS28, 28-joint disease activity score; DMARD, disease-modifying antirheumatic drug; eGFR, estimated glomerular filtration rate calculated with the modification of diet in renal disease (MDRD) method; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire – Disability Index; LBM, lean body mass; LDL, low-density lipoprotein; MTX, methotrexate; RA, rheumatoid arthritis; SDAI, simplified disease activity index; TNF, tumor necrosis factor.

[a]Stage I/II vs. III/IV.

$$P_i = \theta_1 \times [\text{cov}/\text{mean}(\text{cov})]^{\theta 2} \quad (11)$$

where P_i, θ_1, θ_2, and cov are the individual parameter, the population mean parameter with the mean value of the covariate [mean(-cov)], the exponent of the power function, and the covariate, respectively. For categorical covariates, a fractional difference was modeled using a multiplicative function (Equation 12):

$$P_i = \theta_1 \times \theta_3^{\text{COV}} \quad (12)$$

where θ_3 and COV are the coefficient and the class of covariate (yes: COV=1; no: COV=0), respectively. In the final model, the effects of selected covariates on ACR20 response rate and change from baseline in DAS28-CRP were assessed.

In order to assess the influence of each target covariate on the drug effect, the odds ratio (OR) of ACR20 and the change in effect size of DAS28-CRP were calculated and compared to each other using the constructed models, with each mean value of the covariate (mean) or higher value by 1 standard deviation (SD) from the mean (mean+1SD) for continuous covariates, and COV=0 (reference) or COV=1 (with covariate) for categorical covariates. ORs for ACR20 were calculated from probability using Equation 13:

$$\text{OR} = \frac{p_{01(\text{cov}_{\text{mean + 1SD or with covariate}})} / p_{00(\text{COV}_{\text{mean + 1SD or with covariate}})}}{p_{01(\text{cov}_{\text{mean or reference}})} / p_{00(\text{cov}_{\text{mean or reference}})}} \quad (13)$$

The change in effect size of DAS28-CRP was calculated using the simulated DAS28-CRP change from baseline with mean+1SD covariate divided by the simulated change from baseline with mean covariate at week 12, following treatment with peficitinib 150 mg (Equation 14).

$$\text{Change in effect size} = \frac{\text{DAS28} - \text{CRP change from baseline}(\text{cov}_{\text{mean+1SD or with covariate}})}{\text{DAS28} - \text{CRP change from baseline}(\text{cov}_{\text{mean or reference}})} \quad (14)$$

2.6 | Predictive performance

The predictive performance of the final ACR20 and DAS28-CRP models was evaluated by visual predictive check (VPC) using SAS version 9.4 or Perl-speaks-NONMEM version 4.4.8.[20] VPC was constructed based on the parameter estimates of the final model and 1000 datasets generated from the original model.

3 | RESULTS

3.1 | Datasets and demographic summary

Summary statistics of the demographics and baseline disease characteristics of patients are presented in Table 3. The ACR20 dataset included 9912 ACR20-CRP response rate data points from 1057 patients and the DAS28-CRP dataset included 11732 DAS28-CRP data points from 1078 patients.

3.2 | Exposure parameters

The mean (SD, minimum–maximum) individual post hoc $AUC_{24\,h}$ following treatment with peficitinib 25 mg, 50 mg, 100 mg, and 150 mg was 251.9 (43.26, 190.2–415.6), 507.4 (100.0, 342.9–828.1), 1088 (264.6, 533.5–2002), and 1702 (410.7, 752.8–3418), respectively.

3.3 | ACR20 model

The continuous time Markov model was constructed to describe the probability of ACR20 response. The following were defined as target covariates: body surface area (BSA), lean body mass (LBM), prior bDMARD treatment, prior tumor necrosis factor (TNF) inhibitor treatment, total bilirubin, creatinine kinase (CPK), DAS28-CRP, DAS28 based on erythrocyte sedimentation rate (DAS28-ESR), and simplified disease activity index (SDAI). The forward addition step and backward elimination steps revealed that DAS28-CRP and total bilirubin at baseline had a significant effect on EX_{50}, with expression as follows (Equation 15):

$$EX_{50,j} = 693 \times \left(\frac{\text{DAS28} - \text{CRP}_j}{5.3}\right)^{-1.09} \times \left(\frac{\text{total bilirubin}_j}{10}\right)^{-0.445} \quad (15)$$

where DAS28-CRP_j and total bilirubin_j represent the DAS28-CRP and total bilirubin at baseline of the jth subject. The parameter estimates of the ACR20 model are shown in Table 4. The equation for predicted individual EX_{50}, above, indicated that EX_{50} tended to decrease in patients with high DAS28-CRP and total bilirubin levels at baseline. The model predicted ACR20 response rates at 12 weeks for peficitinib 150 mg to be 65.6% and 68.4% with observed mean and mean+1SD DAS28-CRP measurements at baseline of 5.3 and 6.29 in the phase 2 and phase 3 studies, respectively. The model predicted ACR20 response rates to be 65.6% and 67.4% when the observed mean and mean+1SD total bilirubin levels at baseline were 10 μmol/L and 13.8 μmol/L, respectively. The standard error for each parameter was calculated in NONMEM based on an S matrix to converge the covariance step. The VPC plots suggested an adequate predictive performance (Figure 2).

3.4 | DAS28-CRP model

The indirect response model incorporating the effect of drug inhibition on the production rate constant of disease severity was constructed to describe the time course of DAS28-CRP. The target covariates CRP, ESR, DAS28-CRP, DAS28-ESR, SDAI, RA duration, concomitant csDMARD treatment, concomitant methotrexate (MTX) treatment, and inadequate response to prior MTX treatment were selected. The forward addition step and backward elimination steps revealed that CRP at baseline and concomitant MTX treatment had a significant effect on EX_{50} (Equation 16):

$$EX_{50,j} = 3630 \times \left(\frac{\text{CRP}_j}{25}\right)^{-0.218} \times (0.653)^{\text{MTXCD}_j} \quad (16)$$

TABLE 3 Demographics and baseline disease characteristics

	RAJ1 (n = 281)	RAJ3 (n = 307)	RAJ4 (n = 518)
Treatment, n (%)			
Placebo	56 (19.9)	101 (32.9)	170 (32.8)
Peficitinib 25 mg	55 (19.6)	N/A	N/A
Peficitinib 50 mg	57 (20.3)	N/A	N/A
Peficitinib 100 mg	55 (19.6)	104 (33.9)	174 (33.6)
Peficitinib 150 mg	58 (20.6)	102 (33.2)	174 (33.6)
Female, n (%)	228 (81.1)	228 (74.3)	364 (70.3)
Region, n (%)			
Japan	281 (100)	251 (81.8)	518 (100)
Korea	N/A	32 (10.4)	N/A
Taiwan	N/A	24 (7.8)	N/A
Age, mean (SD) [range] (years)	53 (11.5) [21–75]	55.1 (12.2) [22–86]	56.7 (11.6) [20–83]
Body weight, mean (SD) [range] (kg)	56.67 (11.52) [29.9–101]	58.71 (12.25) [32–96.5]	58.16 (12.7) [33.8–117.4]
BSA, mean (SD) [range] (m^2)	1.58 (0.186) [1.1–2.19]	1.61 (0.198) [1.16–2.16]	1.60 (0.201) [1.15–2.42]
LBM, mean (SD) [range] (kg)	42.0 (6.79) [26–68.4]	43.3 (7.48) [28–68.2]	43.2 (7.51) [27.4–70.2]
BMI, mean (SD) [range] (kg/m^2)	22.6 (4.09) [13.4–40.7]	23.25 (4.12) [13.3–36.4]	23.01 (4.51) [14.4–43.1]
Creatinine kinase, mean (SD) [range] (U/L)	67.7 (67.9) [10–808]	67.0 (48.8) [15–457]	61.9 (40.9) [10–368]
Lymphocytes, mean (SD) [range] (10^6/L)	1612.1 (588.1) [400–4100]	1557.7 (499.6) [700–3900]	1502.9 (543.5) [400–4600]
eGFR, mean (SD) [range] (ml/min/1.73 m^2)	92 (21.36) [48–188.4]	87.84 (23.53) [38.5–169.4]	92.82 (21.85) [36.4–175.5]
Total bilirubin, mean (SD) [range] (μmol/L)	10.4 (3.41) [3.42–22.2]	9.82 (3.59) [1.7–22.2]	10.5 (3.60) [3.4–27.4]
DAS28-CRP, mean (SD) [range]	5.28 (1.01) [2.5–8.5]	5.37 (0.99) [2.6–8.0]	5.33 (0.91) [1.9–7.8]
DAS28-ESR, mean (SD) [range]	5.98 (0.96) [2.8–9.1]	5.99 (1.08) [3.1–8.6]	5.95 (0.96) [1.6–8.6]
SDAI, mean (SD) [range]	33.2 (12.4) [6.29–86.5]	34.4 (12.8) [7.7–80.3]	33.5 (11.8) [6.01–74.8]
RA duration, mean (SD) [range] (years)	7.23 (6.32) [0.5–35.7]	8.71 (7.44) [0.4–46.9]	4.36 (2.99) [0.4–10.1]
CRP, mean (SD) [range] (mg/L)	24.12 (24.5) [0–126]	23.86 (24.73) [0.4–169.6]	25.3 (21.34) [0.1–118]
ESR, mean (SD) [range] (mm/h)[c]	48 (24.8) [0–138]	49.4 (28.2) [3–150]	51.9 (26.6) [2–140]
Concomitant csDMARDs at baseline, n (%)	0 (0)	267 (87.0)	518 (100)
Concomitant MTX at baseline, n (%)	0 (0)	125 (59.3)	513 (99.0)
Prior biological DMARDs use, n (%)	83 (29.5)	38 (12.4)	98 (18.9)
Prior TNF inhibitors treatment, n (%)	71 (25.3)	30 (9.77)	78 (15.1)
Inadequate response to prior MTX treatment, n (%)	151 (53.7)	222 (72.3)	518 (100)

Abbreviations: BMI, body mass index; BSA, body surface area; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; DAS28, 28-joint disease activity score; eGFR, estimated glomerular filtration rate calculated with the modification of diet in renal disease (MDRD) method; ESR, erythrocyte sedimentation rate; LBM, lean body mass; MTX, methotrexate; RA, rheumatoid arthritis; SD, standard deviation; SDAI, simplified disease activity index; TNF, tumor necrosis factor.

where CRP_j and $MTXCD_j$ represent the CRP level and concomitant MTX treatment at baseline of the j^{th} subject. The parameter estimates of the DAS28-CRP model are shown in **Table 5**. The equation for predicted individual EX_{50}, above, indicated that EX_{50} tended to decrease for patients with high CRP at baseline and concomitant use of MTX. The model predicted that typical DAS28-CRP changes from baseline at 12 weeks for peficitinib 150 mg were −1.8 and −1.9 with an observed mean and mean+1SD CRP level at baseline of 25 mg/L and 47.7 mg/L in the phase 2 and phase 3 studies, respectively. The model-predicted DAS28-CRP changes from baseline were −1.8 and −2.2 without and with concomitant use of MTX, respectively. The standard error for each parameter was calculated in NONMEM based on an S matrix to converge the covariance step. The VPC plots suggested an adequate predictive performance (Figure 3).

3.5 | Comparison of the effect of target covariates

The following 15 covariates were selected as target covariates in the ACR20 model or DAS28-CRP model: BSA; LBM; total bilirubin; CPK; CRP; ESR; DAS28-CRP; DAS28-ESR; SDAI; RA duration; prior bDMARD treatment; prior TNF inhibitor treatment; concomitant csDMARD treatment; concomitant MTX treatment;

TABLE 4 Parameter estimates of the ACR20 model

Parameter	Estimate	SE	RSE	Variability[a]	Shrinkage
Intercept of λ_{01}	−3.02	0.0829	2.7%	—	—
Intercept of λ_{10}	−1.41	0.0944	6.7%	—	—
EX_{50} (ng.h/mL)	693	62.2	9.0%	—	—
E_{max}	2.56	0.219	8.6%	—	—
K_{eq}	0.120	0.0127	10.6%	—	—
Hill coefficient	2.05	0.460	22.4%	—	—
Covariate, DAS28-CRP on E_{max}	−1.09	0.188	17.2%	—	—
Covariate, total bilirubin on E_{max}	−0.445	0.0950	21.3%	—	—
Random effect of IIV on λ_{01}	1.91	0.210	11.0%	239.9%	26.1%

Abbreviations: ACR, American College of Rheumatology; CRP, C-reactive protein; DAS28, 28-joint disease activity score; E_{max}, maximum effective response; EX_{50}, half-maximal effective area under the concentration–time curve for 0–24 h after dosing; K_{eq}, equilibrium rate constant to reach the steady-state effect; OFV, objective function value; RSE, relative standard error; SE, standard error; λ_{01}, transition constant for transitions from state 0 to state 1; λ_{10}, transition constant for transitions from state 1 to state 0; ω^2, diagonal elements of variance–covariance matrix of random effects on subject-level parameters.

[a]Interindividual variability (IIV) was calculated as $\sqrt{(\exp(\omega^2)-1)\times 100}$ (%), OFV=7158.399.

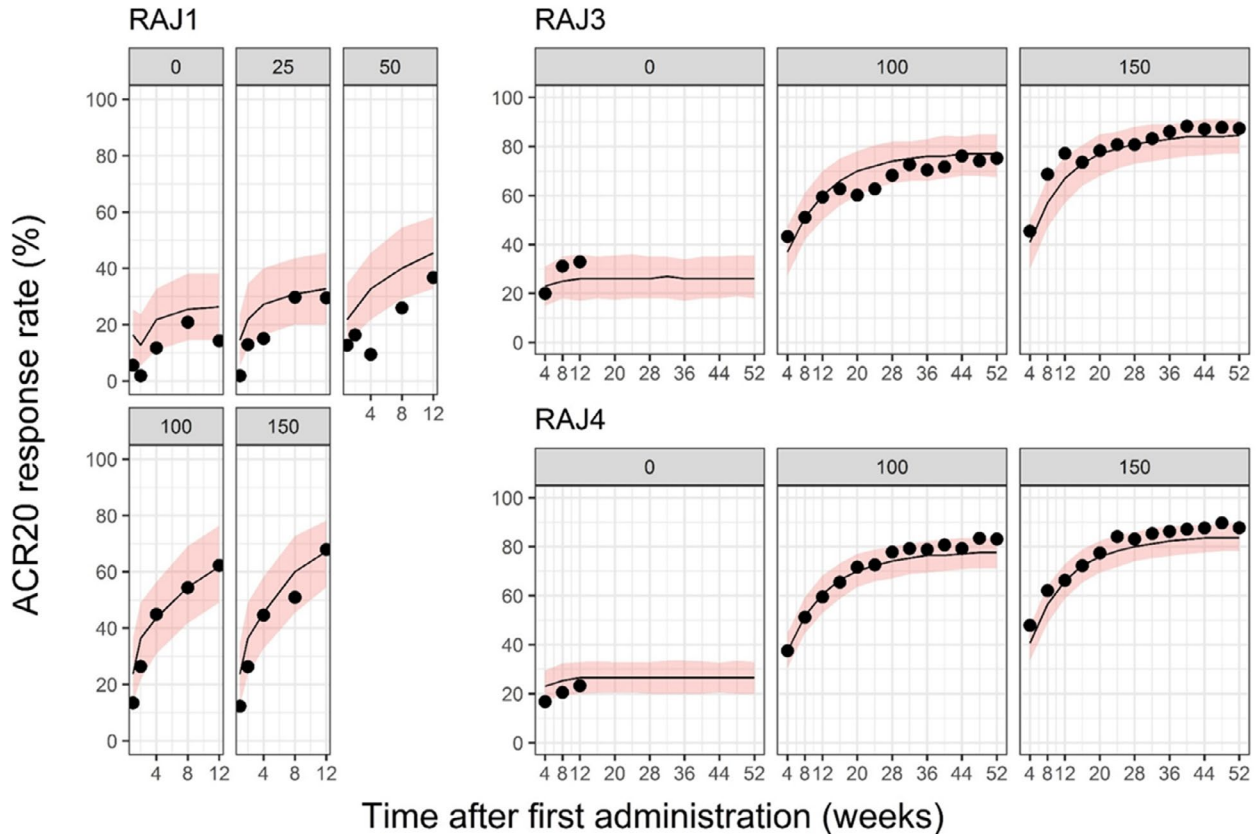

FIGURE 2 Visual predictive check of the ACR20 model. Black circles, observed response rate in each clinical study; black solid curve and pink area, the median and 2.5th/97.5th percentiles of the simulated data, respectively. ACR, American College of Rheumatology; RAJ1, phase 2 study; RAJ3 and RAJ4, phase 3 studies

TABLE 5 Parameter estimates of the DAS28-CRP model

Parameter	Estimate	SE	RSE	Variability[a]	Shrinkage
PA	−0.782	0.0430	5.5%	—	—
Placebo rate constant	0.369	0.0117	3.2%	—	—
EX_{50} (ng/mL)	3630	363	10.0%	—	—
Production rate constant	0.0816	0.00110	1.3%	—	—
Covariate, CRP on E_{max}	−0.218	0.0433	19.9%	—	—
Covariate, concomitant MTX on E_{max}	0.653	0.0725	11.1%	—	—
Random effect of IIV on PA	1.04	0.0570	5.5%	135.2%	11.2%
Random effect of IIV on EX50	1.10	0.0889	8.1%	141.6%	31.0%
Additive residual error	0.538	0.00170	0.3%	—	6.0%

EX_{50}, half-maximal effective area under the concentration–time curve for 0–24 h after dosing; E_{max}, maximum effective response; MTX, methotrexate; OFV, objective function value; PA, maximum placebo effect; RSE, relative standard error; SE, standard error; ω^2, diagonal elements of variance–covariance matrix of random effects on subject-level parameters.

[a]Interindividual variability (IIV) was calculated as $\sqrt{(\exp(\omega^2)-1)\times 100}$ (%), OFV=1832.829.

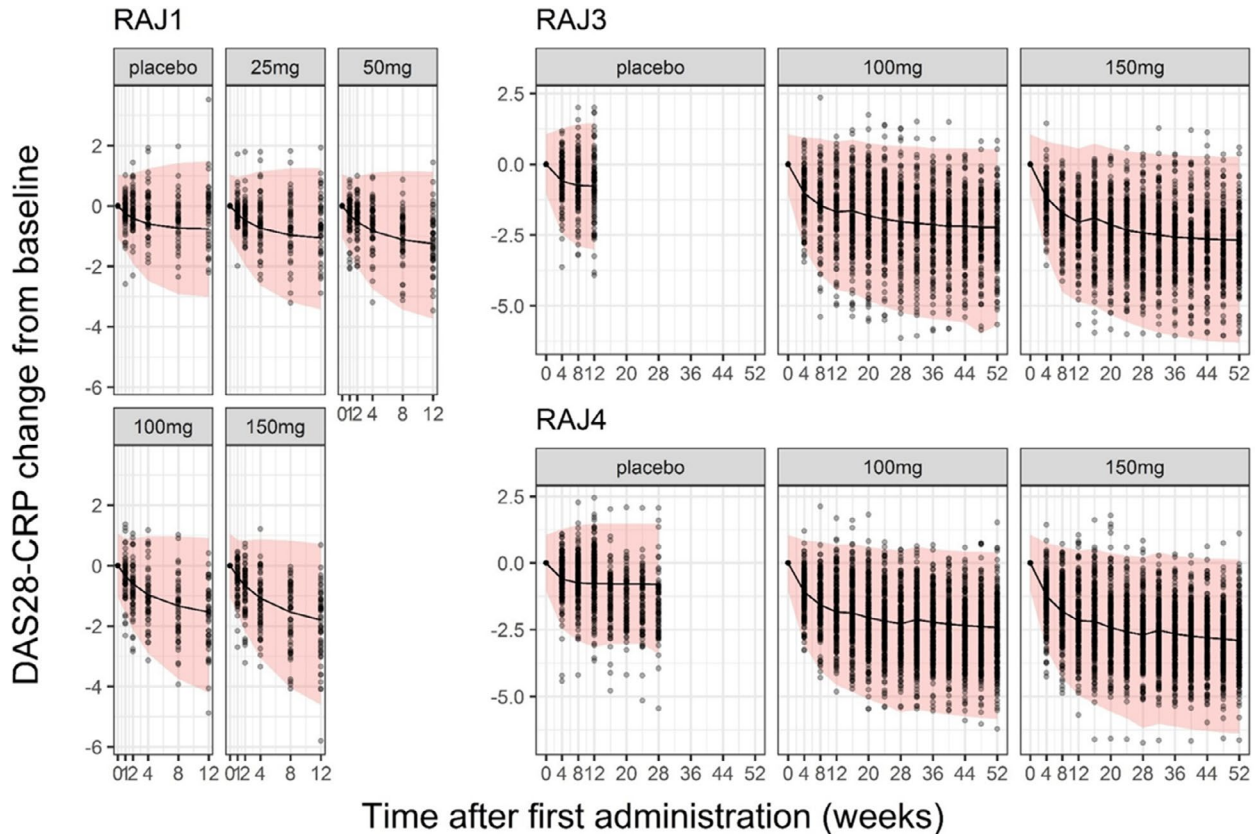

FIGURE 3 Visual predictive check of the DAS28-CRP model. Black circles, observed response rate in each clinical study; black solid curve and pink area, the median and 2.5th/97.5th percentiles of the simulated data, respectively. CRP, C-reactive protein; DAS28, 28-joint disease activity score; RAJ1, phase 2 study; RAJ3 and RAJ4, phase 3 studies

and an inadequate response to prior MTX treatment. The relationship between the ORs of ACR20 response and changes in effect size of DAS28-CRP by the selected covariates on EX_{50} was strongly correlated, as shown in Figure 4.

4 | DISCUSSION

This report is the first analysis to characterize the exposure–response relationships for ACR20 response rate and DAS28-CRP

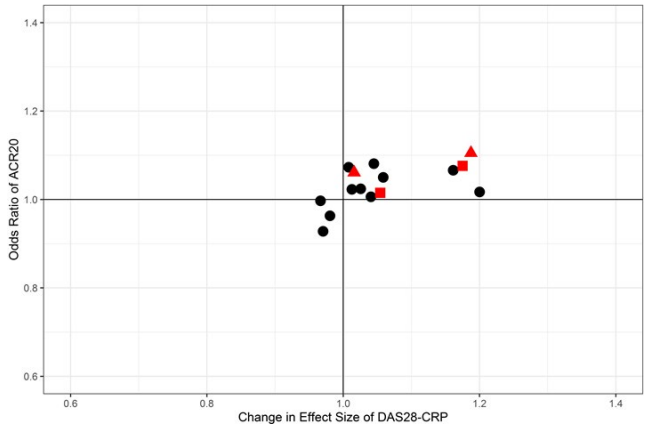

FIGURE 4 Correlation of effects on EX50 by target covariates between ACR20 and DAS28-CRP models. Red triangles, covariates selected in ACR20 model; red squares, covariates selected in DAS28-CRP model; black circles; other target covariates. ACR, American College of Rheumatology; CRP, C-reactive protein; DAS28, 28-joint disease activity score; EX50, drug exposure in $AUC_{24\,h}$ to provide the half-maximal effect

measurements in patients with RA after once-daily administration of peficitinib. A previous phase 2 study identified a dose response for the efficacy of peficitinib in patients with moderate-to-severe RA[9]; similarly, phase 3 studies enrolling patients with RA and an inadequate response either to prior DMARDs[10] or methotrexate treatment[11] showed that efficacy outcomes tended to be numerically higher with peficitinib 150 mg versus 100 mg. This trend was observed consistently across the phase 2 and phase 3 studies with both the ACR20 response rate and change from baseline in DAS28-CRP. By developing an exposure–response model, the magnitude of covariate effects could be explored to inform the optimal use of peficitinib in patients with RA.

ACR20 response rate is treated as a binary categorical variable (response vs. non-response). In order to model binary categorical variables, a logistic regression model with generalized estimating equations can be used,[21] as has been applied previously in the development of models for ACR20 response rates following tofacitinib and baricitinib treatment.[22,23] A continuous time Markov model has the advantage of enabling serial correlation to be modeled within subjects when observations are taken at irregular time points[18]; a continuous time multistate Markov model has previously been used to develop an exposure–response model based on data from certolizumab pegol clinical trials in RA patients and to describe the dynamics of diarrhea events in patients treated with a combination of lumretuzumab and pertuzumab.[24,25] In the present study, a continuous time Markov model was applied to describe the probability of ACR20 response, which decreased the OFV significantly compared with a logistic regression model without considering any association between consecutive responses by Markov element. Moreover, the significant improvement in OFV by introducing a higher p_{01} (the probability of transition from non-response state to a response state) applied at measurements up to 4 weeks after first administration of study drug suggested that an individual's ACR20 response just after the start of treatment could be raised by the patient's subjective high expectations of treatment in a clinical trial. This view may be supported by the recommendation that new DMARD treatments should be continued at least for 3–6 months for exact evaluation of their efficacy.[26] VPC showed that the model generally captured the observed time course for ACR20 response rate.

The indirect response model[19] was applied to describe the time course profile of DAS28-CRP. VPC strongly suggested that the model predictions were consistent with the observed data. The placebo effect could be adequately estimated by including additive IIV to describe both upward and downward time courses found in the placebo treatment group.

The finding that covariates relating to severity of RA, namely DAS28-CRP or CRP levels at baseline, were identified as significant covariates in both the final ACR20 and DAS28-CRP models indicated that baseline severity of disease correlated with the magnitude of the antirheumatic treatment response; this observation was similar to the previous findings for an etanercept ACR20 response model and an abatacept DAS28-CRP model.[27,28] During covariate exploration using the DAS28-CRP model, CRP level at baseline was selected rather than DAS28-CRP, with the lowest OFV in the first forward addition step, while DAS28-CRP at baseline was not selected in the second forward addition step due to moderate correlation with CRP level (r = 0.51). Moreover, concomitant use of MTX treatment was selected as a significant covariate on EX_{50} in the final DAS28-CRP model, which indicated that concomitant use of MTX increased the response. Considering that the peficitinib package insert carries the precaution that the product should be used in patients who have previously been treated with at least one antirheumatic drug, including methotrexate, but apparently still have disease-attributed symptoms, the concomitant use of MTX with peficitinib is feasible. On the other hand, the mechanism behind the significant effect of baseline total bilirubin in the final ACR20 model was unknown, as it was not selected as a significant covariate in a previous population PK model of peficitinib.[17] The simulation results using our final ACR20 and DAS28-CRP models suggested no requirement for dose adjustment based on DAS28-CRP, concomitant MTX treatment, CRP, or total bilirubin at baseline. Caution should be used when applying these models to predict covariate effects in non-Asian patients, as the models were constructed using PK data from an Asian population.

A guidance document for developing drug products for RA treatment from the United States Food and Drug Administration[29] suggests that continuous efficacy variables, such as DAS28, may be more sensitive in terms of assessing the dose response in efficacy and are recommended over dichotomous endpoints, such as ACR20 response. Achieving precision of model estimates for ACR20 response rate was generally challenging compared to the continuous variable of DAS28-CRP.[30] In this analysis, the two separately constructed models for each of ACR20 response and DAS28-CRP provided not only a good description of observed treatment response over time, but also consistent results regarding the effect of

covariates on EX_{50}: measurements of baseline disease severity were selected as significant covariates in both models, and target covariates had similar magnitudes of effect on the OR in the ACR20 model and on changes in effect size in the DAS28-CRP model. The trend of covariate effects showed the similarity between two models, which is to be expected considering that both parameters are key efficacy variables for RA treatment. On the other hand, the difference between these two models was that only the ACR20 model could incorporate a patient's subjective expectation of a positive result just after the start of the treatment.

In conclusion, exposure–response models of peficitinib efficacy in RA patients for time courses of ACR20 response rates and DAS28-CRP measurements were constructed using a continuous time Markov model and an indirect response model. The covariates selected for the model suggested that the baseline severity of disease correlated with the magnitude of the antirheumatic treatment response. Considering the similarities and differences between the two, both the ACR20 response rate model and DAS28-CRP model may have relevant applications for the development of RA treatment.

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CONFLICT OF INTEREST

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A Kaibara was a full-time employee of Astellas Pharma Inc., Tokyo, Japan, at the time of analysis. He is currently a full-time employee of Eli Lilly Japan K.K., Tokyo, Japan.

AUTHOR CONTRIBUTIONS

J.T. wrote the article. All authors were involved with revising this article. J.T., M.S., T.N., and A.K. planned the analysis, and J.T. conducted the analysis. Y.K. was the lead statistician responsible for data handling for each study. H.I. was the study leader for peficitinib and contributed to the planning and conduct of the clinical studies.

DATA AVAILABILITY STATEMENT

Researchers may request access to anonymized participant-level data, trial-level data and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx

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